WASHINGTON UNIVERSITY NEUROFIBROMATOSIS (NF) CENTER

Exceptional Care *through* Groundbreaking Research

2021 ANNUAL REPORT

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MESSAGE FROM THE DIRECTOR

As we conclude our second year of physical distancing, wearing masks, and adapting to virtual interactions, we reflect back on how much we have accomplished in the face of adversity and change. In the Washington University NF Center, we have developed new programs, made impactful research advances, and expanded our clinical care team.

ADVANCING CLINICAL CARE

This year, we welcomed Dr. Jonathan Tiu, Assistant Professor in Neurology, to our clinical care team. Dr. Tiu is partnering with us to provide greater access to care for adults with NF. He is working closely with Dr. Angela Hirbe, Director of the Adult NF Clinical Program, and Dr. Stephanie Morris, Director of the Pediatric NF Clinical Program, to create a seamless transition for our families from St. Louis Children's Hospital to Barnes-Jewish Hospital. Under their leadership, we have provided increasing numbers of families with both telemedicine and in-person clinic consultations.

In addition, Dr. Angela Hirbe and her colleagues have made seminal advances in the genetics and early detection of cancers in adults with NF1. She and Dr. Aadel Chaudhuri developed a new blood test for distinguishing benign plexiform neurofibromas from malignant peripheral nerve sheath tumors (MPNSTs). Moreover, she identified a new protein important for MPNST spread, as well as a common genetic alteration in all MPNSTs.

Working with a large international team, Dr. Gutmann contributed to the establishment of revised criteria for NF1 and Legius syndrome – an important milestone in providing uniform standards for the diagnosis of these conditions. Similarly, Dr. Gutmann and his colleagues worldwide performed the first integrated molecular and clinical analysis of low-grade brain tumors in children with NF1, providing a clear picture of the genetics of these common pediatric cancers.

Lastly, together with Dr. Mohamed Abdelbaki, Chief of Pediatric Neuro-Oncology at St. Louis Children's Hospital, we have created an international virtual NF tumor board, where we provide consultations on clinical management with colleagues in the Middle East and eleven countries worldwide.

ADVANCING NF RESEARCH

In the laboratory, there were numerous exciting advances. Dr. Nicole Brossier (Instructor, Pediatric Hematology and Oncology) defined some of the reasons why only some children with NF1 develop optic gliomas. Using mice with NF1 patient *Nf1* mutations, she showed that a number of critical conditions must be established in order for tumors to form. In addition, Dr. Michelle Wegscheid published a seminal study demonstrating that nerve cell abnormalities in NF1 patients with total gene deletions result from loss of a new gene located within the *NF1* locus. Importantly, she showed that children with NF1 who have a mutation in this gene have higher autism burden. Moreover, Drs. Amanda Costa and Jit Chatterjee found a new population of cells in mouse and human NF1 brain tumors, which formed the basis for new immune-based treatments for *Nf1* optic gliomas.

Working with Dr. Lu Le and his postdoctoral fellows, Dr. Juan Mo, at the University of Texas-Southwestern, Dr. Corina Anastasaki developed the first human neurofibroma mouse model using NF1 patient cells. Additionally, Dr. Yuan Pan, former Gutmann laboratory postdoctoral fellow and current trainee with Dr. Michelle Monje at Stanford University, collaborated with the Gutmann laboratory to demonstrate that nerve cell activity is required for mouse *Nf1* optic glioma formation. In this study, she showed that *Nf1* optic glioma-prone mice raised in the dark did not develop brain tumors, suggesting new potential therapies for these common pediatric cancers.

We have also been fortunate to attract several new members to our research team, including Anna Wilson (future MD-PhD trainee), Dr. Rasha Barakat (new postdoctoral fellow), Dr. Savannah Sims (new postdoctoral fellow), and Dr. Francesca Manzella (new postdoctoral fellow). We also congratulate Ms. Kelly Hartigan, former post-baccalaureate student in the Gutmann laboratory, on her acceptance into the physician-scientist training program at Indiana University.

We also launched our NF Scholars Program, made possible by generous support from Strides4NF. Five undergraduates are currently participating in this program, which aims to provide a complete experience for Washington University students interested in careers in science and medicine.

RAISING NF AWARENESS

Since the Fall of 2020, our Complementary Care Programs and tours have been using a combination of virtual and small in-person group activities with COVID-19 safety precautions in place. In addition, with the growth of our programs, we expanded our Beat NF session opportunities to include a Summer program, and added our first annual NF Center Summer Camp. Partnering with the St. Louis Science Center, this Summer Camp focuses on children with NF1 ages 9-16, combining the motor skills focus of Club NF and the social skill focus of Teen NF.

Sincerely,

David H. Gutmann, MD, PhD, FAAN, FANA
Donald O. Schnuck Family Professor
Director, Washington University NF Center

RESEARCH GRANTS

THE NEUROFIBROMATOSIS THERAPEUTIC ACCELERATION PROGRAM

- awarded **DR. NICOLE BROSSIER** the prestigious Francis S. Collins Scholar Award. Dr. Brossier joins Dr. Hirbe as the second Washington University NF Center recipient.

THE ST. LOUIS MEN'S GROUP AGAINST CANCER

- awarded **DR. ANGELA HIRBE** a fourth one-year grant to continue her important work on malignant cancers in adults with NF1. Dr. Hirbe's laboratory is generating a collection of human malignant peripheral nerve sheath tumors (MPNSTs) suitable for preclinical drug testing.

IAN'S FRIENDS FOUNDATION

- awarded **DR. DAVID GUTMANN** a one-year grant to engineer human skin cells to form humanized brain tumors in mice as an initial step towards the generation of human low-grade brain tumor models for preclinical drug testing.

Photo Credit: Matt Miller

PATIENT SPOTLIGHT: *CARTER HOSS*

Carter Hoss is a goofy, caring, and fun-loving sixth grader. He has also raised over $1500 to benefit NF Midwest through participation in the organization's annual Walk 4 NF event. Both aspects of Carter stem from his drive to constantly improve himself and the world around him, always on a mission to help however he can.

Carter first visited the Washington University NF Clinic Program at St. Louis Children's Hospital as a toddler after his pediatrician referred him to Dr. David H. Gutmann. At this time, he received a diagnosis of NF1. Since then, Carter has been an enthusiastic participant in Club NF, the Washington University NF Center's school-aged free therapy program – he has enjoyed going ice-skating and swimming in particular.

Carter prefers to be active and outside, playing baseball, basketball, soccer, and nerf games with his little brother. He always looks forward to fishing for catfish with his grandpa or baking with his grandma, and has a particular passion for meeting new people and trying new things. He is a reliable friend to his classmates, often standing up for his peers in the face of bullying and serving as a go-to resource for anyone who needs a laugh. When Carter's little brother was nervous for his first day of Kindergarten, Carter reassured him, wisely remarking that everyone has to start somewhere. His mom describes him as "ready to defeat the world."

It was that caring and go-getter attitude that spurred Carter's participation in Walk 4 NF. Walk 4 NF is an annual fundraising event held in several midwestern locations. Its mission is to end NF by funding research and raising awareness. Participants put together their own fundraising teams before coming together to walk, enjoy live music, hear speeches, and connect with other members of the NF community.

Carter's team, called Carter's Cardinals, first participated in Walk 4 NF in 2020. Though that event was virtual, Carter hugely enjoyed the strong sense of community and belonging it generated and was super excited to be featured in an official NF Midwest video played at the event's conclusion.

For the 2021 Walk 4 NF, held in Columbia, MO, Carter increased his fundraising goal, motivated both by the opportunity to help the NF community and his ambition to outdo himself. Not only did Carter meet his goal, but he also won second place in fundraising overall, raising more than twice his original objective. Additionally, he interacted with over 200 people in the NF community - he loved talking with a diverse group of individuals affected by NF, especially those older than him, with wisdom to share. Carter's parents particularly enjoyed talking to other parents of children with NF, exchanging stories and advice. Carter and his family are determined to continue their participation in Walk 4 NF for years to come – where Carter will focus on raising a little bit more every year.

For Carter and his family, the joy of participation in both Walk 4 NF, and Club NF comes from the sense of community present in these events and the feeling of accomplishment that they offer. Carter walks away knowing that he produced tangible change, that he actually did something, and that he is never alone in doing so. For these reasons, the Hoss family strongly encourages all families affected by NF to get involved, both in these events and in all others like them. As put by mother, Moriah, knowing that the money goes "toward something near and dear to our hearts" is the ultimate reward.

INTERNATIONAL EXPERTS REVISE THE NF1 DIAGNOSTIC CRITERIA

A collaboration of international experts has recently reached a consensus for revising the diagnostic criteria of NF1. The method for determining the new measures included a Delphi method involving global experts. Additionally, non-NF experts, patients, and advocacy groups were invited to participate in the evaluation process. The consensus results have determined the minimal clinical and genetic criteria to diagnose NF1 and Legius Syndrome. This report was published in *Genetics in Medicine.*

PROVIDING EXCEPTIONAL PATIENT CARE

NF CENTER AND CHILDREN'S TUMOR FOUNDATION (CTF) SYNODOS TEAM PUBLISH LANDMARK GENOMIC STUDY OF NF1 BRAIN TUMORS

Dr. Michael Fisher at Children's Hospital of Philadelphia and Dr. David Gutmann from the Washington University NF Center spearheaded an internal consortium effort to define the genetics of low-grade brain tumors in children with NF1.

In their study, involving 25 centers worldwide, they characterized the genetic changes seen in these tumors, and analyzed the importance of these alterations to patient outcome. Low-grade gliomas from 70 children with NF1 were studied, revealing additional genetic changes beyond *NF1* gene mutation. One of these changes involving a mutation in the fibroblast growth factor receptor (FGFR1) was shown to increase the growth of *Nf1*-mutant mouse tumor cells.

This report was recently published in *Acta Neuropathologica.*

THE NF CENTER WELCOMES FACULTY MEMBER: DR. TIU

Dr. Jonathan Tiu received his medical degree from Tulane University in New Orleans and completed his Adult Neurology residency at New York University School of Medicine. Dr. Tiu is interested in how neurologic conditions impact everyday function, and divides his time between Neurofibromatosis, General Neurology and Neurorehabilitation at The Rehabilitation Institute of St. Louis. Dr. Tiu joins us in the Washington University NF Center, where he sees adults with Neurofibromatosis.

NF CLINICAL TRIALS CONSORTIUM IDENTIFIES A NEW THERAPY FOR PLEXIFORM NEUROFIBROMAS

A recent study spearheaded by Dr. Michael Fisher at Children's Hospital of Philadelphia, Dr. D. Wade Clapp at Indiana University, and Dr. Amy Armstrong, found that cabozantinib is an effective therapy for NF1-associated plexiform neurofibromas.

Using a preclinical mouse model of plexiform neurofibromas, this team showed cabozantinib was effective at reducing mouse tumors. Leveraging these exciting findings, they launched a Phase II study in patients older than 16 years of age with progressive or symptomatic plexiform neurofibromas. They found that no patient had continued tumor growth on cabozantinib, and many reported reduced pain symptoms.

This landmark study underscores the importance of preclinical models to the identification of promising therapies for patients living with NF1 tumors.

The report was recently published in *Nature Medicine.*

MICHELLE WEGSCHEID, MD, PHD

Neurodevelopmental disorders are often caused by losses of large pieces of chromosomes containing many genes. This is also true for a subset of individuals with Neurofibromatosis type 1 (NF1) who have severe developmental delays and intellectual disabilities. These NF1 patients often harbor a large deletion involving the *NF1* gene on chromosome 17q11.2, termed a total gene deletion (*NF1*-TGD).

To understand why children with this chromosomal deletion have such profound neurological deficits, Dr. Michelle Wegscheid, a former MD-PhD student in the laboratory of Dr. David Gutmann, teamed up with her colleagues in the NF Center to use patient-derived human induced pluripotent stem cells (hiPSCs) to generate cerebral organoids (hCOs) or "mini-brains".

In a new report recently published in the journal *Cell Reports,* Dr. Wegscheid, along with Dr. Corina Anastasaki, Kelly Hartigan, Olivia Cobb, Jennifer Traber, and Dr. Stephanie Morris, identified both neural stem cell growth and neuronal maturation abnormalities in *NF1*-TGD hCOs. While the increased NSC proliferation resulted from decreased *NF1*/RAS regulation, they showed that the neuronal differentiation, survival and maturation defects were caused by reduced expression of a gene called cytokine receptor-like factor 3 (CRLF3).

Importantly, they demonstrated a higher autism burden in NF1 patients harboring a mutation in the *CRLF3* gene, thus establishing CRLF3 as a new causative gene within the *NF1*-TGD locus responsible for hCO brain abnormalities and autism in children with NF1.

A YEAR OF GROUNDBREAKING RESEARCH

During 2021, researchers in the Washington University NF Center made many groundbreaking discoveries. Additionally, we continue to expand the resources required to make these advances, including the NF1 Genome Project (~589 patient DNA samples), NF1 Clinical Research Database (~820 patients enrolled), and the NF1 Brain Trust (~35 patient stem cell lines). These critical resources only exist because of the enthusiastic involvement of our families.

LU LE, MD, PHD

In a recent study published in the *Journal of Clinical Investigation,* Dr. Lu Le, Professor of Dermatology at the University of Texas-Southwestern, joined forces with Drs. Corina Anastasaki and David Gutmann at the Washington University NF Center to develop a human model of neurofibroma. By taking advantage of human stem cell engineering methods, called CRISPR, the team developed a series of NF1 patient-specific human induced-pluripotent stem cells (hiPSCs), which they used to create human Schwann-like cells. They found that implanting human NF1 Schwann-like cells in the nerves of mice resulted in the formation of bona fide neurofibromas, thus creating the first human model of this common tumor.

Together, these two laboratories established complementary humanized neurofibroma explant and first-in-kind mouse genetically engineered cutaneous neurofibroma model amenable to future therapeutic target discovery and evaluation.

NICOLE BROSSIER, MD, PHD

In a recent study published in *Neuro-Oncology,* Dr. Nicole Brossier, who is a pediatric neuro-oncologist specializing in the care of children with NF1-associated brain tumors, showed that the cells which likely give rise to optic gliomas in mice with *Nf1* mutations exhibit different capacities to grow as a function of the type of germline *Nf1* gene mutation, the age of the mouse, and the location of the cells in the brain. Her detailed work demonstrates that *Nf1* brain tumor formation in mice must occur during embryonic development, in specific progenitor cells in the brain, and in mice with some, but not all, germline *Nf1* gene mutations.

Seeing, hearing, thinking, daydreaming — doing anything at all, in fact — activates neurons in the brain. But for people predisposed to developing brain tumors, the ordinary buzzing of their brains could be a problem. A study by researchers at Washington University School of Medicine in St. Louis and Stanford University School of Medicine shows that the normal day-to-day activity of neurons can drive the formation and growth of brain tumors.

The researchers studied mice genetically prone to developing tumors of their optic nerves, the bundle of neurons that carries visual signals from the eyes to the brain. The mice served as a model for children with the genetic condition Neurofibromatosis Type 1 (NF1). About one in six children with NF1 develops low-grade optic nerve tumors by age 7. In this study, mice with *Nf1* mutations raised under normal lighting developed tumors; those kept in the dark during a critical period of development did not.

The findings, published May 26 in the journal *Nature,* suggest that neuronal activity plays an underappreciated role in nervous system cancers. The research opens up new avenues to preventing brain tumors in children at high risk for them.

Co-senior author Michelle Monje, MD, PhD, an associate professor of neurology at Stanford Medicine, previously demonstrated that neuronal activity drives the growth of an aggressive form of brain cancer. But it wasn't clear whether neuronal activity itself sets in motion the process of tumor formation or if it only bolsters the growth of tumors initiated by other processes.

As part of this study, the researchers used mice with mutations in their *Nf1* gene. Such mice start developing low-grade tumors of their optic nerves around 9 weeks of age, and virtually all have tumors by 12 weeks to 16 weeks old. Since the neurons in the optic nerve become active when exposed to light, the researchers investigated whether they could reduce neuronal activity — and, thereby, tumor formation — simply by keeping the mice away from light. They raised mice from age 9 weeks to 16 weeks in the dark and then checked for tumors.

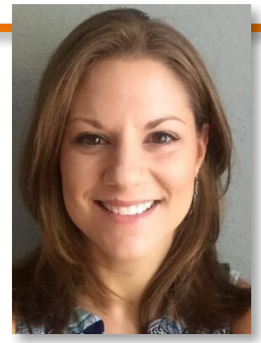
Further experiments verified the crucial role of light exposure and narrowed down the critical window to age 6 weeks to 12 weeks. None of the mice reared in the dark during that time frame developed tumors by 24 weeks of age. Putting mice older than 12 weeks, when the tumors already had formed, into darkness slowed tumor growth but did not shrink them.

First author Yuan Pan, PhD, who first worked with Gutmann at Washington University and is now a postdoctoral researcher with Monje, showed that the link between light and tumors requires a protein called neuroligin 3. When their optic nerves are stimulated, mice with *Nf1* mutations release abnormally high levels of neuroligin 3. Blocking the protein with a drug or genetically modifying mice to eliminate the neuroligin 3 gene resulted in fewer and smaller tumors.

"All of this is teaching us that we may have ignored one really important cell type in nervous system cancers: the neuron," said co-senior author David H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor of Neurology at Washington University and the director of the university's NF Center. "As neurologists, we have been treating overactive neurons for decades with drugs. One of the directions our laboratories are pursuing is repurposing some of those drugs to see if we can shut off unwanted activity, maybe just for a short developmental period, and prevent brain tumors from forming. And there are other points at which we could intervene as well: by limiting light exposure, by targeting neuroligin 3 or inhibiting some other step in the pathway. It has really opened our eyes."

Originally written by Tamara Bhandari. Washington University School of Medicine: The Record, May, 26, 2021.Edited for space.

SUSAN E. MALONEY, PHD



As part of an investigation into shared motor impairments across genetic liabilities for intellectual and developmental disorders (IDDs), a research group led by Drs. Susan Maloney and Joseph Dougherty, in collaboration with the Gutmann laboratory, recently discovered altered gait development in mice harboring a patient-derived *Nf1* gene mutation. This new study conducted a comprehensive analysis of gait across a critical developmental window in which gait matures in the mouse model. *Nf1* mutant mice exhibited altered spatial, temporal, and postural subcomponents of gait compared to their control littermates, which persisted into adulthood. In addition, the pattern of disruption to gait development in this *Nf1* model was also observed in a mouse model of Williams Syndrome, another IDD that features motor deficits. Overall, their findings indicate that IDDs may share features of atypical gait yet differ in resolution or persistence of these abnormalities. Therefore, gait may serve as a helpful outcome variable in studies of therapeutic efficacy in the long-term treatment of IDDs.

SUPPORT BEYOND THE CLINIC

MEET MAKENZIE SLEDD
PHYSICAL THERAPIST FOR THE NF CENTER PROGRAMS

A wife, a mother of two kiddos herself, and a physical therapist at St. Louis Children's Hospital, Makenzie has been practicing since 2008 following graduation from St. Louis University with a master's degree in Physical Therapy.

Makenzie has extensive experience in providing continuity of care, consultations, and education to patients and families. She thrives in a multidisciplinary environment where she has the opportunity to collaborate with occupational and speech therapists, and Washington University physician teams. She has spent her career not only working directly with patients, but also with physicians in Orthopedics, Neurology and Hematology.

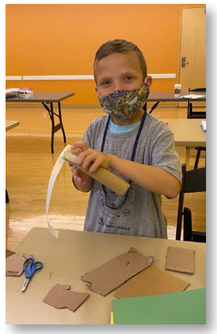
She has developed and streamlined physical therapy protocols and teaching tools for her department to use, while fostering continuity of care between therapists and improving patient outcomes. Additionally, she has developed departmental resources that provide therapists and parents with a centralized repository of educational resources and information. Makenzie loves to share these resources and information with other therapists, patients, and families.

Makenzie approaches her practice by looking at the entire picture. She believes in looking beyond the medical diagnosis and treating the whole patient – even if that means spending an extensive amount of personal time and energy researching problems outside of the realm of physical therapy. She tries to make sure that her families have all of the information and resources they need to best care for themselves.

The highlight of Makenzie's summers is her long tenure as co-director of the Gateway Hemophilia Association Camp Notaclotamongus. In response to the 2020 COVID-19 pandemic, Makenzie led the team in pivoting their programming to a virtual setting to optimally serve the kids she adores so much. She also is a member of the National Hemophilia Association Physical Therapy Working Group, which plans and executes the annual NHF Bleeding Disorder Conference. Recently, she has helped form an organization, from the bottom up, composed of physical therapists across the country to continue her work to share knowledge and create resources to better the management of patients. Makenzie considers all of these activities a "pastime" and in essence, her passion for pediatric health does not fall far from her personal life.

Although it's nearly impossible for Makenzie to turn off her "PT Brain", she enjoys unwinding with her husband and two daughters by gardening, crafting, camping, and hiking. Through Makenzie's Motor Minute, Makenzie will address a variety of topics that support children with NF achieve the best versions of themselves.

NF CENTER SUMMER CAMP



In collaboration with the St. Louis Science Center, the Washington University NF Center held its first annual NF Center Summer Camp. The program, designed for children with NF1 ages 9-16, focused on social, executive function, gross motor, and fine motor skills.

With the theme for the 2021 Summer Camp centering around space, activities included building stomp rockets and Alka-Seltzer rockets, flying a drone, creating a constellation wheel, an Egg Drop Parachute contest, and sampling astronaut food. The participants of this event had the St. Louis Science Center all to themselves, as this two-day event was held in person while the facility was closed to the public. Additionally, strict COVID-19 safety protocols were followed throughout the two days.

COMPLEMENTARY CARE PROGRAMS

At the Washington University NF Center, we believe that the care of our families extends beyond the walls of the hospital. To supplement our medical services at St. Louis Children's Hospital, we have partnered with the St. Louis Children's Hospital Foundation, Jazz St. Louis, and the St. Louis Science Center to create complementary care programs for all age groups that address the ongoing needs of children with NF1.

BEAT NF (Ages 2 – 5 years)

Together with Jazz St. Louis education staff, the Washington University NF Center has developed this one-of-a-kind therapy program that specifically focuses on frequently delayed skills in young children with NF1. During each session, professional jazz musicians play live music, while the children review social engagement rules as a group, learn about a "mystery instrument", and engage in gross and fine motor therapy. Educators and musicians from Jazz St. Louis compose and play original music expressly written for these activities. In addition, Beat NF Team members carefully design each week's program to work on particular social and motor delays in toddlers with NF1.

During each session, toddler participants enjoy five weeks of a jazz music motor therapy curriculum utilizing jazz music and physical therapy to promote social, attention, and motor skills in toddlers with NF1, while also fostering healthy parent-child interactions, peer relationships, and jazz appreciation.

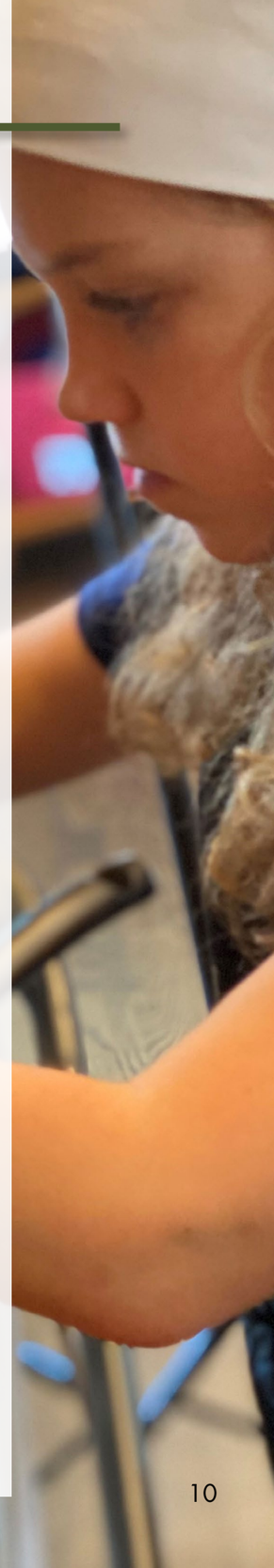
CLUB NF (Grades K – 8)

Through our partnership with St. Louis Children's Hospital, the Washington University NF Center proudly provides Club NF as a free, bimonthly, play-based therapy program for children with NF1. Each event is designed to address a specific set of skills often delayed in school age children with NF1. While children are working on those skills with their therapists, parents have the opportunity to speak with NF specialists to learn more about NF1 and to implement the strategies used in Club NF activities.

Club NF aims to empower families and children with NF1 through the use of play-based therapy and education. By creating a safe, fun environment, families with NF1 learn more about this condition, as well as understand how to foster healthy communication and interactions with peers. Past virtual Club NF events include: Schnucks Cooking School, Katmai National Park Ranger Talk and JR Ranger Badge, and JR Vet Lab with the Loggerhead Marinelife Center.

TEEN NF (Ages 13 – 18 years)

Our Teen NF program, led by St. Louis Children's Hospital neuropsychologist Dr. Kimberly Sirl, is open to all teenagers with NF1, with the objective of fostering positive interpersonal relationships at home, at school and in the community. Focusing on common challenging social situations that teens encounter, the goal of this program is to further social and conversational skills, encourage appropriate selection of friends, learn to read social cues, and enter/exit conversations with peers. Additionally, the program has been expanded to include peer support, social interaction opportunities used to practice learned social skills, and leadership development through volunteer opportunities. Partnering with the St. Louis Science Center, Teen NF also offers Life Skills and Career Building classes, to help prepare patient families for adulthood.



nfcenter.wustl.edu

As we celebrate our successes in 2021 and look forward to 2022, we want to thank everyone who has supported our mission. We are particularly indebted to our partners at the St. Louis Children's Hospital Foundation and Schnuck Markets Inc.
Washington University NF Center 2021 Annual Report created and designed by Jennifer N. Traber.